UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: **12/14/2015**

SUBJECT: **Fenbuconazole.** Human Health Assessment Scoping Document in Support of Registration Review.

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Attached is the Health Effects Division's (HED) human health risk assessment scoping document for the fungicide fenbuconazole to support registration review.

Executive Summary

The Health Effects Division (HED) Fenbuconazole Registration Review Team has evaluated the Agency's databases and the most recent human health risk assessment for fenbuconazole. HED performed this evaluation in order to determine the scope of work necessary to support the established tolerances and existing registrations during registration review. The primary sources of information are the most recent human health risk assessment for a proposed increase in the tolerance on peppers in 2013 (D403401), and the HED Hazard and Science Policy Committee (HASPOC) reviews of the need for subchronic inhalation toxicity, acute/subchronic neurotoxicity and immunotoxicity studies (TXR Nos. 0056540 and 0056730, respectively).

Fenbuconazole is a broad-spectrum fungicide of the triazole (conazole) chemical class. It is currently registered for use on the following food/feed crops: almonds, apples, bananas, bushberries (subgroup 13B), citrus fruits (group 10), cranberries, pecans, peanuts, peppers, stone fruits (group 12), sugar beets and wheat. Tolerances are established for the combined residues of fenbuconazole and its lactone metabolites, expressed as parent, in/on plant commodities at levels ranging from 0.05 ppm (almonds and pecans) to 40 ppm (citrus oil) [40 CFR 180.480(a)]. At present there are no registered residential uses.

The toxicological database is complete and considered adequate to assess the human exposure and estimated health risks from currently registered uses. The HED HASPOC recommended that acute and subchronic neurotoxicity, subchronic inhalation toxicity and immunotoxicity studies are not needed based on a weight of evidence consideration of toxicological, physico-chemical, structure-activity relationship and exposure data. The liver is the major target organ in all species tested. The thyroid is also a target organ in the rat, secondary to changes in liver metabolic capacities. Neurotoxicity and immunotoxicity were not observed in the available studies, and no systemic toxicity from dermal exposure was observed in rats tested up to the limit dose. A toxicological mode of action in mammals has not been identified at this time.

The 10x FQPA safety factor for fenbuconazole has been reduced to 1x since there are no residual uncertainties for pre- and/or post-natal toxicity. There is no evidence for increased susceptibility following *in utero* exposure to rabbits, or following pre/postnatal exposure to rats in a two-generation reproduction study. Increased qualitative susceptibility was seen in the rat developmental toxicity study (fetal effects were more severe than maternal effects). However, the concern is low for this observation, since developmental effects are well characterized and show clear NOAELs and LOAELs, and the developmental NOAEL is used as the point of departure (POD) for acute dietary risk assessment. Other PODs selected are also protective of these effects. Exposure estimates are not likely to underestimate risk associated with registered uses.

Fenbuconazole is classified (1986 Cancer Guidelines) as a Group C, or possible human carcinogen, based on an increased incidence of liver tumors in mice and thyroid tumors in rats. Cancer risk assessments (dietary and occupational) have been conducted based on the cancer potency factor derived from the incidence of liver tumors in female mice. For occupational cancer risk from dermal and inhalation exposure, absorption was considered 4.25% (rat *in vivo* dermal absorption) and 100% of the oral dose, respectively.

Current doses and endpoints, safety factors and cancer risk are not expected to change during registration review. However, they will be reviewed to ensure they are consistent with current science policies and guidance (e.g., to ensure proper characterization of toxicological effects, identification of NOAELs and LOAELs, etc.).

The database for residue chemistry and dietary exposure assessment, including food and drinking water, is considered complete and no additional studies are required at this time. Analytical methods available for enforcement of the currently established tolerances are adequate. No risks of concern, including cancer risk, have been identified for dietary exposure to fenbuconazole. An updated dietary exposure assessment may be required during registration review if new toxicological points of departure (PODs), cancer potency factor or safety factors, are selected, new data become available that impact dietary exposure assessment (including for residues in drinking water), or if policies and procedures for dietary exposure assessment are revised.

There are no registered residential products for fenbuconazole nor are the registered use sites likely to result in use by the residential/consumer market or by commercial applicators to residential sites. However, a risk assessment will be completed during registration review that addresses the potential exposure from spray drift and volatilization.

No aggregate non-cancer or cancer risks (food and drinking water) of concern have been identified. An updated aggregate exposure assessment should be conducted if a new dietary exposure assessment is conducted, including the potential for an updated drinking water assessment, or if a residential assessment is required at the time of registration review.

Assuming that the recently submitted dislodgeable foliar residue (DFR) study is found to be acceptable, the database for assessing risk from occupational exposure to fenbuconazole is considered complete and no additional data are required at this time. Exposures to occupational handlers is of short- and intermediate-term duration. No risks of concern for short/intermediate-term exposure, or cancer risk, have been identified for occupational (inhalation) handler or post-application exposure; per product labels, risks were estimated assuming no respirators are worn. Subsequent to the most recent occupational exposure assessment, there have been changes to the Agency's policies related to occupational exposure assessment. During registration review, updated non-cancer occupational handler and post-application exposure assessments will be prepared that incorporate the latest policies. Changes in toxicological PODs, cancer potency factor or safety factors, if any, will also be incorporated at that time.

A cumulative assessment is not required for fenbuconazole. A common mechanism of toxicity has not been established for the conazole (triazole) chemical class of fungicides. HED has previously assessed dietary risk from the triazole-derived metabolites, 1,2,4-triazole and its conjugates triazolylalanine and triazolylacetic acid, resulting from exposure to conazole fungicides as a group. The need for an updated 1,2,4-triazole dietary assessment will be determined at the time of registration review.

Differences in international tolerance definitions for residues of concern have been identified. Tolerances in the U.S. are established for residues in numerous crops and livestock commodities.

Residues of concern for enforcement are the parent fenbuconazole and two of its metabolites (RH-9129 and RH-9130). The Canadian residue definition is the same, but differences in residue definition exist for Mexico and Codex (parent fenbuconazole only). During registration review, HED will reevaluate U.S. tolerances for fenbuconazole and, to the extent possible, harmonize them with Codex MRLs.

Introduction

HED has evaluated the most recent human health risk assessment for fenbuconazole (D403041; memorandum dated January 31, 2013), in association with updates to its toxicity, exposure and usage databases, to determine if sufficient data are available, and if further updates are needed, to support registration review. This risk assessment evaluated a proposed increased tolerance on peppers, updating the assessment for a new use on peppers (D344351, memorandum dated June 12, 2008).

Fenbuconazole (alpha-(2-(4-chlorophenyl)-ethyl)-alpha-phenyl-3-H(1H-1,2,4-triazole)-1-propanenitrile) is a broad-spectrum fungicide of the triazole (conazole) chemical class. The structure and chemical and physical properties may be found in Attachment 1. It is registered for use on a variety of crops: almonds, apples, bananas, bushberries (subgroup 13B), citrus fruits (group 10), cranberries, pecans, peanuts, peppers, stone fruits (group 12), sugar beets and wheat. There are two end-use products: a flowable concentrate formulation (EPA Reg. No. 62719-416) and a wettable powder in water soluble packet formulation (EPA Reg. No. 62719-421) applied at rates from 0.06 to 0.188 lb ai/acre depending on the crop. Tolerances are established (based on parent fenbuconazole and metabolites RH-9129 and RH-9130, expressed as fenbuconzole) for these commodities as primary crops only, as well as meat byproducts of cattle, horses, goats and sheep.

Hazard Identification/Toxicology

The toxicology database for fenbuconazole is considered complete and no additional toxicology studies are needed at this time (see Toxicity Profile, Attachment 2, for a complete summary of the toxicology database). The HED Hazard and Science Policy Committee (HASPOC) recommended that (1) acute and subchronic neurotoxicity studies are not required because neurotoxicity is not anticipated to be the most sensitive effect and (2) a subchronic inhalation study is not required because inhalation MOEs using an oral POD were sufficiently high (i.e., $\geq$1000)(TXR No. 0054540). Based on lack of immunotoxicity in the conazole fungicides as a chemical class, HASPOC recommended that an immunotoxicity study is not needed for these compounds (TXR No. 0056730).

Fenbuconazole is rapidly absorbed, distributed and excreted following oral exposure (83-93% of dose by 96 hrs) following single or repeated dosing in the rat. Elimination was primarily via the feces (76-84%), due largely to biliary excretion, with 6-13% excreted in the urine. Plasma levels peaked at 3-6 hr and bioaccumulation in tissues was not observed. Extensive metabolism was observed. Quantitative but not qualitative differences in metabolite levels were observed between males and females.

The liver is the main target organ following subchronic or chronic exposure. At lower dose levels, effects are limited to increased liver weight and hepatocellular hypertrophy, changes which are considered to be adaptive. Adverse effects are observed at higher dose levels and include alterations in clinical chemistry and histopathological changes such as hepatocellular vacuolization and necrosis. A mode of action (MOA) for liver toxicity of fenbuconazole has not been established. Although conazoles have related structures and commonly show liver toxicity, other effects vary and a common MOA for mammalian toxicity, including toxicity to the liver, has not been established. However, total dietary exposure to 1,2,4-triazole and other common metabolites may occur and has been assessed by the Agency (see Cumulative Assessment section, below).

In the rat, thyroid follicular cell hypertrophy was observed along with increased thyroid and parathyroid weights and alterations in thyroid hormone levels. These effects are considered secondary to the effects on the liver, resulting in alterations in the homeostatic balance between the pituitary and thyroid. Increased adrenal and kidney weights were also seen in the dog following chronic exposure, and decreased body weights were also seen in several studies. There was no evidence of neurotoxicity or immunotoxicity. Toxicity was not observed in the rat following a subchronic dermal exposure. A dermal absorption factor (DAF) of 4.25% was selected based on the maximum absorption observed in a rat *in vivo* dermal absorption study.

HED reduced the 10x FQPA Safety Factor (FQPA SF) to 1x. Fetal effects in the rat and rabbit developmental studies were observed at doses causing maternal toxicity. In the rat developmental toxicity study, increased post-implantation loss and decreased live fetuses per dam were noted at a dose level at which decreased maternal body weight and body weight gain were observed. In the rabbit developmental study, maternal toxicity was based on decreased food consumption and clinical signs, observed at a lower dose level than the developmental toxicity, which was based on increased early resorptions. A second, more recent rabbit study identified similar maternal effects, along with decreased fetal body weight. In the rat two-generation reproduction study, decreased mean pup body weight, an increased number of stillborn pups, decreased number of total offspring delivered, and decreased pup viability index were seen at the same dose level that produced maternal death and decreased maternal body weights. Reproductive toxicity was not observed. There were no residual uncertainties regarding developmental effects, and exposure assessments are not likely to underestimate risks associated with the registered uses. The developmental studies identified well-defined developmental NOAELs and LOAELs and all endpoints selected for risk assessment are protective of developmental toxicity.

Doses and endpoints for risk assessment are summarized in Attachment 3. An appropriate endpoint for the acute dietary reference dose (aRfD) was not identified for the general population, but for females age 13 to 49, an endpoint was identified based on developmental effects in the rat (increased post-implantation loss). The non-cancer chronic reference dose (cRfD) endpoint was based on liver and thyroid effects and decreased body weight in the rat chronic toxicity/carcinogenicity study. A dermal POD was not selected because no toxicity was observed up to the limit dose in the 28-day rat dermal study. The maternal toxicity effects seen in the developmental studies were examined in the dermal study, and therefore it is protective of developmental findings. Furthermore, adjustment of developmental LOAELs with the DAF of

~4% yields doses in excess of the 1000 mg/kg/day limit dose. For inhalation toxicity, the rat 90-day oral toxicity study was selected based on liver, thyroid and body weight effects.

Fenbuconazole is classified as a Group C or possible human carcinogen under the Agency's 1986 Cancer Guidelines, based on the increased incidence of liver tumors in male and female mice and thyroid tumors in male rats. A cancer potency factor of 3.59×10^{-3} was determined based on the incidence of liver tumors in female mice. Fenbuconazole showed no evidence of genotoxicity.

Technical grade fenbuconazole has low acute toxicity (Category III for oral and inhalation toxicity; IV for dermal toxicity). It is not a skin or eye irritant (Category IV) or a dermal sensitizer.

Conclusions for Hazard Identification/Toxicology

The toxicology database for fenbuconazole is adequate to support registration review and no additional toxicology study requirements (under 40 CFR Part 158) are needed. Subchronic inhalation, acute and subchronic neurotoxicity and immunotoxicity studies have not been submitted, but HED has determined that these studies are not needed.

The current PODs and endpoints, safety factors, cancer classification and cancer potency factor are not expected to change during registration review, but should be reevaluated at that time to ensure that they are consistent with science and regulatory policies for assessment of hazard, or if new toxicology data are submitted that impact their selection In addition, the effects used to identify the NOAELs and LOAELs should be reevaluated to make sure they are considered adverse under current HED/OPP scientific policies. An endpoint for incidental oral exposure will be required for assessment of spray drift. PODs and endpoints for residential handler or post-application exposure are not required, unless new proposed residential uses are added, but these would be expected to be the same as those selected for occupational exposure.

Dietary Exposure

Fenbuconazole is registered for use on a wide variety of crops, and permanent tolerances have been established (40 CFR §180.480) ranging from 0.05 to 40 ppm in plant commodities and at 0.05 ppm in livestock commodities. For livestock commodities, only ruminant (goat, sheep, and cattle) and horse, meat and meat byproduct, commodity tolerances have been set; no poultry, pork, eggs, or milk tolerances have been set.

As summarized in Table 1 (below), HED has determined that the residues of concern for risk assessment are fenbuconazole and the following metabolites: RH-9129, RH-9130, RH-4911(peanut only), and RH-7905 (peanut only). Changes to these residues of concern are not anticipated during registration review. For tolerance enforcement, HED has concluded that the residues of concern are parent fenbuconazole, plus RH-9129 and RH-9130. Acceptable analytical methods are available to enforce tolerances for residues of fenbuconazole, as well as RH-9129 and RH-9130, in plant and livestock commodities.

In addition, HED previously concluded that the iminolactone metabolite (RH-6468) would also be included *de facto* in the residues of concern, as the petitioner has indicated that this compound is converted to the lactones by the analytical method.

Furthermore, it is noted that the available poultry metabolism studies were previously deemed inadequate. Based on the currently registered use pattern and the anticipated dietary burden for poultry, additional poultry metabolism data and a poultry feeding study are not needed at this time, nor do tolerances need to be established. Should the use pattern expand in the future and result in a higher than anticipated dietary burden in poultry, this decision may need to be revisited.

Table 1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression*

Matrix		**Residues included in Risk Assessment**	**Residues included in Tolerance Expression**
Plants	Primary Crop	Fenbuconazole + RH-9129 + RH-9130 + RH-7905 (peanut only) + RH-4911 (peanut only)	Fenbuconazole + RH-9129 + RH-9130, expressed as fenbuconazole
	Rotational Crop	Not Applicable	Not Applicable
Livestock	Ruminant	Fenbuconazole + RH-9129 + RH-9130	Fenbuconazole + RH-9129 + RH-9130, expressed as fenbuconazole
	Poultry	Not Applicable	Not Applicable
Drinking Water		Fenbuconazole	Not Applicable

* The common triazole metabolites 1,2,4-triazole, triazolylalanine, and triazolylacetic acid have been identified as residues of concern for risk assessment. Separate assessments addressing these compounds have been conducted (see. T. Morton. D403618. 8/1/2012).

HED used the Dietary Exposure Evaluation Model (DEEM-FCID™ Version 3.16) to conduct the most recent acute, chronic, and cancer aggregate dietary (food and drinking water) risk assessments for fenbuconazole (D403621, D. McNeilly, 01/08/2013). This model uses 2003-2008 food consumption data from the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA). The acute dietary exposure analysis is based on tolerance-level residues and assumes 100% crop treated. The chronic (non-cancer) dietary analysis is more refined because it uses average residues from field trials, but it also assumes 100% crop treated (%CT). The cancer dietary analysis uses the same food residue inputs as those used in the chronic non-cancer assessment. However, the cancer analysis is further refined in that it makes use of average percent crop treated estimates for a number of commodities. The acute, chronic (non-cancer), and cancer assessments use both empirical and default processing factors. No risks of concern were identified in either the non-cancer or the cancer dietary exposure assessments.

The Environmental Fate and Effects Division (EFED) recommended that modeled estimates of residues in drinking water be used in the most recent dietary risk assessment. During registration review, HED will evaluate whether updated drinking water estimates are available and whether these revised estimates make it necessary to complete a new dietary assessment. Depending on the magnitude of any updates, a new dietary assessment may be required to appropriately estimate risks associated with drinking water exposure.

Conclusions for Dietary Exposure

The dietary exposure database is adequate to support the existing registrations and tolerances. No new residue chemistry data are needed. However, a new dietary assessment may be needed if one or more of the following occur: new data are identified which impact dietary exposure estimates, including those from drinking water; new toxicological points of departure are identified, including revisions to the FQPA SF; Office of Pesticide Programs (OPP) dietary exposure policies and procedures are revised. HED is in the process of updating its dietary model to incorporate more recent consumption data from the National Health and Nutrition Examination Survey (NHANES). The newer version of the model will be used during registration review if a new dietary assessment is needed. Exposure to the triazole metabolites common to the conazole fungicides may also be considered if a new dietary assessment is needed.

Residential Exposure

There are no products containing fenbuconazole registered for residential use, nor are the registered use sites considered likely to result in applications by residential applicators or by commercial applicators to residential sites. During registration review, a residential handler and post-application assessment will not be required unless new residential uses are proposed.

Spray Drift and Volatilization: Residential bystander exposures resulting from off-site transport (e.g., spray drift or volatilization) may occur as a result of applications of fenbuconazole. The potential for spray drift will be quantitatively evaluated for each pesticide during the Registration Review process. In terms of volatilization, the agency has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analyses are required for specific chemicals.

Conclusions for Residential Exposure

There are no proposed or current registrations for products containing fenbuconazole that allow residential use. Therefore, residential handler and post-application exposure assessments will not be needed during Registration Review, unless residential uses are proposed subsequent to this scoping assessment. The need for spray drift and volatilization risk or for residential exposure assessment for fenbuconazole will be examined during Registration Review.

Aggregate Exposure

The most recent aggregate exposure was performed as part of the 2013 human health risk assessment for the proposed increased tolerance on peppers, using modeling to assess acute, chronic and cancer aggregate dietary exposure to fenbuconazole. As there are no registered residential uses of fenbuconazole, aggregate exposure is equivalent to dietary exposure from food and drinking water. No risks of concern were identified for dietary non-cancer exposure and risk estimates, which were well below HED's level of concern of 100% of the aPAD (at

2.9%) and cPAD (at 2.9% for the general population and 6.7% for children 1-2 years of age, the most highly exposed group). Cancer risk was estimated at 2.2×10^{-6}. Actual cancer risk is likely to be much lower, because residue inputs based on field trial data and the assumption of upper bound %CT are expected to overestimate dietary exposure.

Conclusions for Aggregate Exposure

No risks of concern were identified for the general U.S. population or any population subgroup. At the time of registration review, HED will conduct a new aggregate risk assessment that will be based on any policy changes, updates to toxicological PODs or updated exposure estimates from food, drinking water and, if necessary, residential exposure.

Occupational Exposure

There are two end-use products of fenbuconazole registered for application to numerous crops (see above): a flowable concentrate formulation (EPA Reg. No. 62719-416) and a wettable powder in water soluble packet formulation (EPA Reg. No. 62719-421) applied at rates from 0.06 to 0.188 lb ai/acre depending on the crop. Applications are made using aerial, groundboom, and airblast equipment. Chemigation can be used for cranberries only.

Based on the registered use patterns, dermal and inhalation exposures during the application process (i.e., mixing/loading, applying) are expected. In addition, exposures are also expected from entering areas previously treated with fenbuconazole.

Occupational Handlers: Assessments for occupational handler exposure were completed in 2006 to address the original Section 3 registration of both products (D328908) and in 2008 and 2013 to address additional uses on peppers (D345898 and D404874). Exposures to occupational handlers is of short- and intermediate-term duration. In all previous assessments dermal toxicity was not identified, therefore non-cancer dermal risks were not quantified. Non-cancer inhalation assessments were conducted and no assessment identified any risks of concern, assuming, per product labels, no respirators are worn.. All the previous assessments conducted cancer risk assessments for both dermal and inhalation exposures with results for private farmer-applicators ranging from 6×10^{-9} to 1×10^{-6} and for commercial/contract applicators ranging from 1×10^{-8} to 4×10^{-6}. All assessments considered the label-required work attire and personal protective equipment (PPE) of long pants, long sleeve shirts, shoes/socks, chemical-resistant gloves, and no respirators. In addition, a 2009 special local need (SLN) registration (D366632) granted use of the high application rate (0.188 lb ai/acre) on additional crops and different application methods. Up until that time, that rate was limited to certain crops and application methods. A quantitative occupational handler assessment was not conducted specifically for these uses. During registration review, HED will consider which scenarios need to be re-assessed due to updated body weigh assumptions as well as revised unit exposures, and will also re-assess cancer risk at that time.

The previous risk assessments do not reflect the most up-to-date exposure data or inputs for occupational handlers. During Registration Review, updated occupational non-cancer handler inhalation and dermal and inhalation cancer handler risk assessments will be conducted to reflect

current occupational assessment policies and data sets. In addition, some occupational handler exposure scenarios from the SLN registration will need to be included. Should review of the toxicity database continue to conclude that there is no non-cancer dermal toxicity, a quantitative non-cancer dermal assessment will not be required.

Another objective of Registration Review will be to reconcile handler work attire and PPE with corresponding end-use acute toxicity-based requirements and potential requirements based on the updated risk assessment.

Occupational Post Application: Occupational post-application exposures are possible for workers conducting hand labor activities (e.g., harvesting) following use of fenbuconazole on agricultural crops. In the 2008 risk assessment for fenbuconazole use on peppers and the 2006 assessment addressing the Section 3 uses of fenbuconazole, occupational post-application dermal assessments were conducted for cancer risks only as non-cancer dermal toxicity was not identified. The assessments utilized application rates from 0.06 to 0.188 lb ai/acre depending on the crop. Cancer risks ranged from 1.8×10^{-7} to 3.2×10^{-9}. Similarly a post-application occupational assessment will need to be completed with addresses the use patterns described in the 2009 SLN.

Since completion of the previous assessments there have been various updates to occupational post-application policies and data sources. Because the most recent occupational post-application exposure assessments are not reflective of current exposure policies and data, fenbuconazole exposure scenarios will have to be re-assessed during Registration Review. In addition, some post-application exposure scenarios resulting from the SLN registration will need to be included.

Another objective of Registration Review will be to reconcile restricted entry intervals (REIs) with corresponding active ingredient acute toxicity-based requirements. Current labels specify an REI of 12 hours which is consistent with the current active ingredient acute toxicity profile.

While previous assessments relied on default residue factors, a dislodgeable foliar residue (DFR) study (EPA MRID 45250601) is available for fenbuconazole. The study was submitted in 2000 by Rohm and Haas Company, and examined the dissipation of residues on citrus and apple trees following application of fenbuconazole. This study has not yet been reviewed by HED, nor has it been used in previous assessments. During Registration Review the study will be reviewed and considered for purposes of post-application dermal exposure assessment. If this study is found to be acceptable, it would satisfy the CFR Part 158 requirement for DFR studies when a pesticide has occupational uses that could result in post-application dermal exposure.

Additionally, based on the Agency's routine practices, a quantitative occupational post-application inhalation exposure assessment was not performed for fenbuconazole in the previous assessments. There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The agency sought expert advice and input on issues related to volatilization

of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for fenbuconazole.

Conclusions for Occupational Exposure

The occupational exposure database is adequate to support the Registration Review process for fenbuconazole and no additional studies are needed at this time if the submitted DFR study is found to be acceptable. The most recent occupational handler and post-application exposure assessments are not reflective of current exposure policies and data. During Registration Review, updated occupational handler and post-application assessments should be conducted to reflect current policies and data, any updates to the toxicity database, and use of the available DFR study.

Public Health and Pesticide Epidemiology Data

For this evaluation, both the OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) databases were consulted for pesticide incident data on the active ingredient fenbuconazole (D427829, memorandum dated September 1, 2015). Fenbuconazole is not included in the Agricultural Health Study (AHS), and therefore the study does not provide information for this report.

For the main IDS (consisting of incidents with higher severity outcomes and with more details regarding case specifics), incidents reported from January 1, 2010 to May 27, 2015 were reviewed. There were no incidents reported for the single chemical fenbuconazole, and 1 incident reported involving more than one chemical, classified as moderate severity. In the Aggregate IDS (consisting of incidents resulting in less severe outcomes listed as minor, unknown or no effects), there were 2 incidents reported involving fenbuconazole.

The SENSOR-Pesticides database consists of incident data from 12 states collected from 1998-2011 from sources that include local Poison Control Centers, state Department of Labor workers' compensation claims as reported by physicians, State Departments of Agriculture reports and physician reports to state Departments of Health. Incidents reported in this database are primary occupational but also include non-occupational. Six incidents were reported involving fenbuconazole, one of which was a single chemical exposure characterized as a low severity occupational case in which gastrointestinal and neuromuscular symptoms were reported upon reentry to a treated orchard after the 12 hour reentry interval.

Based on the low frequency and severity of incident cases reported for fenbuconazole in both IDS and SENSOR-Pesticides there does not appear to be a concern at this time that would warrant further investigation. The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be included in the risk assessment.

Tolerance Assessment and International Harmonization

As stated above, fenbuconazole is registered for use on a wide variety of crops, and permanent tolerances have been established (40 CFR §180.480) ranging from 0.05 to 40 ppm in plant commodities and at 0.05 ppm in livestock commodities. For livestock commodities, only ruminant (goat, sheep, and cattle) and horse, meat and meat byproduct, commodity tolerances have been set; no poultry, pork, eggs, or milk tolerances have been set. HED has determined that the residues of concern for risk assessment are fenbuconazole and the following metabolites: RH-9129, RH-9130, RH-4911(peanut only), and RH-7905 (peanut only). For tolerance enforcement, HED has concluded that the residues of concern are parent fenbuconazole, plus RH-9129 and RH-9130. Acceptable analytical methods are available to enforce tolerances for residues of fenbuconazole in plant and livestock commodities. The current tolerance definition for fenbuconazole (40 CFR 180.480) is appropriate regarding scope and compliance.

The residue definition for both Codex and Mexico is fenbuconazole, and the Canadian residue definition is the combined residues of fenbuconazole and its metabolites, RH-9129 and RH-9130, each expressed as parent (*i.e.*, the same as the U.S. tolerance definition).

The Codex MRL for pepper is 0.6 ppm and was most likely established before the Enable 2F formulation was proposed for use on peppers, and includes only residues of the parent compound. This new formulation has higher residues values ranging up to 0.7 ppm, and does include the two lactone metabolites. Harmonization with the 0.6 ppm tolerance is not feasible given the registered use pattern in the U.S. There is no extant Canadian or Mexican MRL, for fenbuconazole on peppers, and thus there are no harmonization issues in North America.

The international residue limit status sheet can be found in Attachment 4.

During registration review, HED will reconsider the U.S. tolerances and will harmonize them with Codex MRLs to the extent possible. This U.S. tolerance review will include assessing whether it is appropriate to update and convert specific crop group tolerances to be consistent with current crop groupings.

International or Intergovernmental Work Sharing

At present the Agency has no worksharing efforts underway for fenbuconazole. The European Food Safety Authority prepared its "Conclusions on the Peer Review of the Pesticide Risk Assessment of the Active Ingredient Fenbuconazole (EFSA Journal 2010 8(4):1558; http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/1558.pdf). The Authority stated that "No areas of concern were identified in the mammalian toxicology section" or "…in the residue section." Regarding dietary exposure, the report stated that "No risk was identified for consumers, but this evaluation has to be considered provisional, since the

contribution of the triazole-derivative metabolites (TDMs) was not taken into account." The Food and Agriculture Organization of the United Nations (FAO/JMPR) evaluated the toxicology of fenbuconazole in 1997 (http://www.inchem.org/documents/jmpr/jmpmono/v907pr07.htm) and identified an ADI of 0.03 mg/kg bw/day. The Canadian Pesticide Management Regulatory Agency (PMRA) and the California Department of Pesticide Regulation (CDPR) are not currently assessing the human health risk for fenbuconazole.

Cumulative Risk Assessments

Fenbuconazole is a member of the triazole-containing class of pesticides. Although conazoles act similarly in fungi by inhibiting ergosterol biosynthesis, there is not necessarily a relationship between their pesticidal activity and their mechanism of toxicity in mammals. Structural similarities do not constitute a common mechanism of toxicity. Evidence is needed to establish that the chemicals operate by the same, or essentially the same, sequence of major biochemical events (EPA, 2002). In conazoles, however, a variable pattern of toxicological responses is found. Some conazoles are hepatotoxic and hepatocarcinogenic in mice. Some induce thyroid tumors in rats, and some induce developmental, reproductive and neurological effects in rodents. Furthermore, the conazoles produce a diverse range of biochemical events, including altered cholesterol levels, stress responses and altered DNA methylation. It is not clearly understood whether these biochemical events are directly connected to their toxicological outcomes. Thus, there is currently no evidence to demonstrate that conazoles share common mechanisms of toxicity and EPA is not following a cumulative risk approach based on a common mechanism of toxicity for the conazoles. For information regarding EPA's procedures for cumulating effects from substances found to have a common mechanism of toxicity, see EPA's website at http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides.

Application of fenbuconazole also results in potential exposures to the metabolites T (1,2,4-triazole), TA (triazolylalanine), TAA (triazolylacetic acid), and THP (triazolyl hydroxypropionic acid). These compounds are considered to be toxicologically different from tetraconazole. HED recently conducted an aggregate risk assessment for these compounds with the resulting exposure estimates less than HED's level of concern (D426493, T. Morton, 9-Apr-2015).

Fenbuconazole is a triazole-derived pesticide. Application of fenbuconazole may result in exposure to the metabolites 1,2,4-triazole, TAA, or triazolylalanine, and THP, or triazolylacetic acid, which are common to this chemical class. These compounds are considered to be toxicologically different from fenbuconazole. To support existing tolerances and establish new tolerances for triazole-derivative pesticides, including fenbuconazole, HED recently conducted an updated aggregate risk assessment of these compounds, with the resulting exposure estimates less than HED's level of concern (D426493, April 9, 2015). As part of registration review, a revised triazole dietary risk assessment may be required.

Human Studies

Previous occupational assessments were completed based on the use of the Pesticide Handlers Exposure Database (PHED) and data from the Agricultural Reentry Task Force (ARTF) which

have been reviewed from an ethics perspective and no issues were found that would preclude its use in the risk assessment process. The occupational assessment for registration review will likely continue to rely in part on the same datasets, but may also rely on newer data sources like the Agricultural Handler Exposure Task Force (AHETF), studies in EPA's 2012 Residential SOPs, or other standalone studies EPA uses to assess residential and occupational exposure. All data sources for occupational exposure assessment have undergone appropriate ethics review, including when applicable, review by the Human Studies Review Board (HSRB).

Data Recommended to be Required

None (presuming acceptability of submitted DFR study)

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Williams-Foy, S. and Rinde, E. (1996) Carcinogenicity Peer Review of Fenbuconazole (2nd), Memorandum dated April 15, 1996. TXR No. 0011894.

Attachments

Attachment 1. Chemical Identity and Physical and Chemical Properties

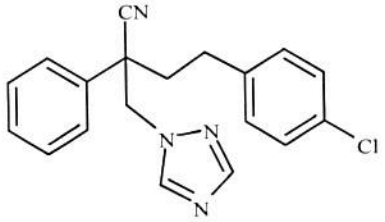
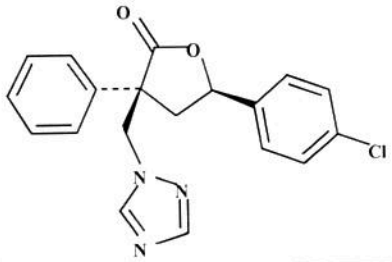
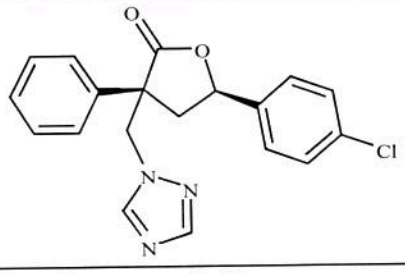
Table 3.1. Nomenclature of Fenbuconazole and its Regulated Metabolites	
Compound	
Common name	Fenbuconazole
Company experimental names	RH-7592
IUPAC name	(*RS*)-4-(4-chlorophenyl)-2-phenyl-2-(1*H*-1,2,4-triazol-1-ylmethyl)butyronitrile
CAS name	α-[2-(4-chlorophenyl)ethyl]-α-phenyl-1*H*-1,2,4-triazole-1-propanenitrile
Chemical class	Conazoles (triazoles)
Molecular weight	336.8
CAS registry number	114369-43-6 (119611-00-6, racemate)
End-use products/EP	2 lb/gal FlC and 75% WPs
Metabolite	
Common name	*cis* lactone metabolite
Company experimental names	RH-9129
IUPAC names	(3R,5R)-5-(4-chlorophenyl)-3-phenyl-3-(1H-1,2,4-triazol-1-ylmethyl)dihydrofuran-2(3H)-one
CAS names	*cis*-5-(4-chlorophenyl)dihydro-3-phenyl-3-(methyl-1-H,2,4-triazole-1-yl-2-(3H)-furanone
Molecular weight	353.8
CAS registry number	146887-38-9
Metabolite	
Common name	*trans* lactone metabolite
Company experimental names	RH-9130

Table 3.1. Nomenclature of Fenbuconazole and its Regulated Metabolites	
IUPAC names	(3S,5R)-5-(4-chlorophenyl)-3-phenyl-3-(1H-1,2,4-triazol-1-ylmethyl)dihydrofuran-2(3H)-one
CAS names	*trans*-5-(4-chlorophenyl)dihydro-3-phenyl-3-(methyl-1-H,2,4-triazole-1-yl-2-(3H)-furanone
Molecular weight	353.8
CAS registry number	146887-37-8

Table 2.3. Physical and Chemical Properties of the Technical Grade Fenbuconazole			Reference
Parameter	Value		
Melting point	126.5–127.0°C		D310959, S. Oonnithan, 7/25/2008
pH	Not available		
Bulk Density	0.50 g/mL		
Water solubility at 22°C	3.8 mg/L		
Solvent solubility (g/L) at 25°C	Acetonitrile 231 Cyclohexanone 445 Ethyl alcohol 39 1-octanol 13	Aromatic 200 77 Ethyl acetate 159 Heptane 1.0	
Vapor pressure at 25°C (PAI)	0.37×10^{-7} mm Hg (4.9×10^{-6}Pa)		
Dissociation constant (pK_a) (PAI)	Not expected to dissociate in water		
Octanol/water partition coefficient $Log(K_{OW})$	$Log(K_{OW}) = 3.22$		
UV/visible absorption spectrum	λ max (nm) 196 262 268 275	ε ($L \cdot mol^{-1} \cdot cm^{-1}$) 53,000 750 740 480	

Attachment 2. Toxicology Profile Tables

Table 4.1 - Acute Toxicity of Fenbuconazole - Technical (shaded) and End-Use (2F, 24% ai) Product

Guideline No.	Study Type	MRID	Results	Toxicity Category
870.1100	Acute Oral - Rats	41031209	Oral LD_{50} (M) > 2000 mg/kg	III
870.1100	Acute Oral - Rats	41031207	Oral LD_{50} (M and F) > 2000 mg/kg	III
870.1100	Acute Oral - Rats	41031221	Oral LD_{50} (M) > 5000 mg/kg	IV
870.1100	Acute Oral - Rats	41031222	Oral LD_{50} (F) > 5000 mg/kg	IV
870.1200	Acute Dermal - Rats	41031208	LD_{50} (M and F) > 5000 mg/kg	IV
870.1200	Acute Dermal - Rats	41031223	LD_{50} (M) > 5000 mg/kg	IV
870.1200	Acute Dermal - Rats	41031224	LD_{50} (F) > 5000 mg/kg	IV
870.1300	Acute Inhalation - Rats	41398201	LC_{50} (M and F) > 2.1 mg/L Particle size too large. Requirement was waived because of a problem in generating respirable dust particles or liquid aerosol.	III
870.1300	Acute Inhalation - Rats	41031225	LC_{50} (M and F) > 2.1 mg/L	III
870.2400	Primary Eye Irritation- Rabbits	41031211	Not irritating to unwashed eyes	IV
870.2400	Primary Eye Irritation- Rabbits	41031226	Not irritating to the eyes	IV
870.2500	Primary Dermal Irritation- Rabbits	41031212	Not irritating to the skin	IV
870.2500	Primary Dermal Irritation- Rabbits	41031227	Not irritating to the skin	IV
870.2600	Dermal Sensitization- Guinea pigs	41031213	Is not a sensitizer under conditions of study.	N/A
870.2600	Dermal Sensitization- Guinea pigs	41031228	Is not a sensitizer under conditions of study.	N/A

Table 4.2 - Toxicity Profile of Fenbuconazole Technical				
Guideline No.	**Study Type**	**MRID**	**Doses**	**Results**
870.3100	90-Day oral toxicity rodents - rats	41073502	0, 20, 80, 400 or 1600 ppm (**Males:** 0, 1.3, 5.1, 25.3 or 103.0 mg/kg/day; **Females:** 0, 1.5, 6.3, 31.1 or 123.9 mg/kg/day)	**NOAEL** = 5.1/6.3 mg/kg/day (M/F) **LOAEL** = 25.3/31.1 mg/kg/day (M/F) based on decreased body weight, liver effects (histopathology, clinical chemistry effects and increased liver weight)
870.3100	90-Day oral toxicity rodents - mice	41073503	0, 20, 60, 180, and 540 ppm (**Males:** 0, 3.8, 11.1, 28.6 or 99.1 mg/kg/day; **Females:** 0, 5.7, 17.6, 50.4 or 139.2 mg/kg/day)	**NOAEL** = 11.1/17.6 mg/kg/day (M/F) **LOAEL** = 28.6/50.4 mg/kg/day (M/F) based on liver histopathology and clinical chemistry changes
870.3150	90-Day oral toxicity in nonrodents - dogs	41073504	0, 30, 100, 400, and 1600 ppm (**Males:** 0, 1.0, 3.3, 13.3 or 50.4 mg/kg/day; **Females:** 0, 1.1, 3.5, 14.0 or 53.3 mg/kg/day)	**NOAEL** = 13.3/14.0 mg/kg/day (M/F) **LOAEL** = 50.4/53/3 mg/kg/day (M/F) based on liver histopathology, clinical chemistry in females
870.3200	21/28-Day dermal toxicity - rats	41875013 42882701	0, 250, 625 or 1000 mg/kg/day	**NOAEL** = 1000 mg/kg/day (HDT) (systemic and local dermal irritation) **LOAEL** = >1000 mg/kg/day (systemic and local dermal irritation)
870.3250	90-Day dermal toxicity	N/A	N/A	Not performed
870.3465	28 or 90-Day inhalation toxicity	N/A	N/A	Not performed
870.3700	Prenatal developmental in rodents - rats	41031214 41073505	0, 30, 75 or 150 mg/kg/day	**Maternal NOAEL** = 30 mg/kg/day **Maternal LOAEL** = 75 mg/kg/day based on decreased body weight and body weight gain during treatment **Developmental NOAEL** = 30 mg/kg/day **Developmental LOAEL** = 75 mg/kg/day based on decreased implantations, increased post-implantation loss and a decrease in the number of live fetuses/dam

Table 4.2 - Toxicity Profile of Fenbuconazole Technical				
Guideline No.	**Study Type**	**MRID**	**Doses**	**Results**
870.3700	Prenatal developmental in nonrodents – rabbits	41875014 42882701	0, 10, 30 or 60 mg/kg/day	**Maternal NOAEL** = 10 mg/kg/day **Maternal LOAEL** = 30 mg/kg/day based on decreased food consumption and increased incidence of clinical signs (soft/scant/no feces and red discharge) during treatment **Developmental NOAEL** = 30 mg/kg/day **Developmental LOAEL** = 60 mg/kg/day based on increased early resorptions
870.3700	Prenatal developmental in nonrodents – rabbits	45259401	0, 15 or 45 mg/kg/day	**Maternal NOAEL** = 15 mg/kg/day **Maternal LOAEL** = 45 mg/kg/day, based on decreased food consumption and increased incidence of clinical signs (scant or no feces) during treatment **Developmental NOAEL** = 15 mg/kg/day **Developmental LOAEL** = 45 mg/kg/day based on decreased fetal body weight

Table 4.2 - Toxicity Profile of Fenbuconazole Technical				
Guideline No.	**Study Type**	**MRID**	**Doses**	**Results**
870.3800	Reproduction and fertility effects - rats	41875015	0, 8, 80 or 800 ppm (0, 0.4, 4 or 40 mg/kg/day)	**Parental systemic NOAEL** = 4 mg/kg/day **Parental systemic LOAEL** = 40 mg/kg/day based on maternal death during delivery, decreased body weight and food consumption, increased number of dams not delivering viable or delivering nonviable offspring, and increased adrenal and thyroid/parathyroid weights **Reproductive NOAEL** = 40 mg/kg/day (HDT) **Reproductive LOAEL** = >40 mg/kg/day **Offspring systemic NOAEL** = 4 **Offspring systemic LOAEL** = 40 mg/kg/day based on decreased mean pup body weight, increased number of stillborn pups, decreased number of total offspring delivered, and decreased viability index
870.4100	Chronic toxicity - rodents			See 870.4300
870.4100	Chronic toxicity - dogs	41875049	0, 15, 150 or 1200 ppm (0, 0.38, 3.75 or 30 mg/kg/day)	**NOAEL** = 3.75/0.38 mg/kg/day (M/F) **LOAEL** = 30/3.75 mg/kg/day (M/F) based on decreased body weight gain **Note:** dose-related adaptive liver changes were observed in high-dose males and females.
870.4200	Carcinogenicity - rats			See 870.4300
870.4200	Carcinogenicity - mice	41893301 41635303	**Males:** 0, 10, 200 or 650 ppm (0, 1.43, 28.6 or 92.9 mg/kg/day) **Females:** 0, 10, 650 or 1300 ppm (0, 1.43, 92.9 or 186 mg/kg/day)	**NOAEL** = 1.43 mg/kg/day (M & F) **LOAEL** = 28.6/92.9 mg/kg/day (M/F) based on decreased body weight, increased relative and absolute liver weight, and hepatocellular hypertrophy and vacuolization *Evidence of carcinogenicity*

Table 4.2 - Toxicity Profile of Fenbuconazole Technical				
Guideline No.	**Study Type**	**MRID**	**Doses**	**Results**
870.4300	Combined chronic toxicity/ carcinogenicity - rat	41635301 41635302	**Control** - 0 ppm **Low** - 4 ppm (weeks 1 & 2), 6 ppm (weeks 3 & 4) or 8 ppm (weeks 5-term) **Mid** - 40 ppm (weeks 1 & 2), 60 ppm (weeks 3 & 4) or 80 ppm (weeks 5-term) **High** - 400 ppm (weeks 1 & 2), 600 ppm (weeks 3 & 4) or 800 ppm (weeks 5-term) (**Males:** 0, 0.31, 3.03 or 30.62 mg/kg/day; **Females:** 0, 0.4, 4.02 or 43.07 mg/kg/day)	**NOAEL** = 3.0/4.0 mg/kg/day (M/F) **LOAEL** = 30.6/43.1 mg/kg/day (M/F) based on decreased body weight gain (F), hepatocellular enlargement and vacuolization (F), increased thyroid weight (M&F), and histopathological lesions in the thyroid gland (M) *Evidence of carcinogenicity*
870.4300	Combined chronic toxicity/ carcinogenicity - rat	42021901 42055001	**Control** - 0 ppm **Low** - 400 ppm (weeks 1 & 2), 600 ppm (weeks 3 & 4) or 800 ppm (weeks 5-term) **High** - 800 ppm (weeks 1 & 2), 1200 ppm (weeks 3 & 4) or 1600 ppm (weeks 5-term) (0, 30.4, and 63.9 mg/kg/day)	**NOAEL** = Not established **LOAEL** = 30.4 mg/kg/day (M) based on decreased body weight gain, increased liver weight, and increased thyroid and parathyroid weights **Note:** only males were used in this study. *Insufficient evidence of carcinogenicity*
870.5100	Gene mutation - bacterial reverse mutation assay	41031216	**TA1535** - 30-300 ug **TA1537** - 30-300 ug **TA98** - 0.2-20 ug **TA100** - 160-1600 ug	No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay. **Note:** only TA1535, TA1537, TA98, and TA100 were tested. This study is classified unacceptable.
870.5100	Gene mutation - bacterial reverse mutation assay	41031217	**TA1535** - 30-300 ug **TA1537** - 30-300 ug **TA98** - 30-300 ug **TA100** - 30-300 ug	No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay. **Note:** only TA1535, TA1537, TA98, and TA100 were tested. This study is classified unacceptable.

Table 4.2 - Toxicity Profile of Fenbuconazole Technical				
Guideline No.	**Study Type**	**MRID**	**Doses**	**Results**
870.5300	Cytogenetics - *in vitro* mammalian cell gene mutation test (CHO Cells)	41031218	15-50 µg/mL without S9 activation 35-60 µg/mL with S9 activation	No increase in mutant frequency at the HGPRT locus, in the presence or absence of S9 activation.
870.5385	Cytogenetics - mammalian bone marrow chromosomal aberration test (rats)	41031219	0, 0.25, 1.25 or 2.5 g/kg	No increase in number of cells with aberrations or in aberrations per cell.
870.5550	Other effects - unscheduled DNA synthesis in mammalian cells in culture (rats)	41031220	0, 7.5, 10.0, 12.5 or 15.0 µg/mL	No evidence (or a dose-related positive response) that unscheduled DNA synthesis was induced.

Table 4.2 - Toxicity Profile of Fenbuconazole Technical				
Guideline No.	**Study Type**	**MRID**	**Doses**	**Results**
870.7485	Metabolism and pharmacokinetics - rat	41875017 41875018	**1)** 1 mg/kg radiolabelled, single dose by oral gavage **2)** 100 mg/kg radiolabelled, single dose by oral gavage **3)** 1 mg/kg unlabelled, 14 days in the diet, PLUS 1 mg/kg radiolabelled, single dose by oral gavage **4)** 1 mg/kg radiolabelled, by i.v. injection	The mean recovery of radioactivity 4 days after exposure was 82.6-93.0% following single or repeated oral doses and 88.2-99.2% following single i.v. doses, indicating rapid absorption, distribution, and elimination. Rapid elimination and low tissue levels indicate low bioaccumulation of the parent and metabolites. Elimination occurred primarily by biliary excretion because recovery of radioactivity was mostly in the feces: 75.6-83.7% following oral exposure and 77.2-91.4% following i.v. exposure. In urine, radioactivity recovery was 5.5-12.6% for all dose scenarios. Peak radioactivity in the blood occurred 3 hours following a single low dose and 3-6 hours after a single high dose, indicating biphasic elimination. Only 8.5-14.8% and 0.0-2.7% of the parent compound was recovered in the feces and urine, respectively, indicating extensive metabolism. A number of major metabolites were identified; however, 50% and 20% of metabolites in the feces and urine, respectively, were not identified. Sex-related differences include a greater number of sulfate metabolites in female excreta compared to males, and a greater number of ketoacid metabolites in male urine compared to female urine.

Table 4.2 - Toxicity Profile of Fenbuconazole Technical				
Guideline No.	**Study Type**	**MRID**	**Doses**	**Results**
870.7485	Metabolism and pharmacokinetics - rat	42900801	1) 1 mg/kg radiolabelled, single dose by oral gavage 2) 100 mg/kg radiolabelled, single dose by oral gavage 3) 1 mg/kg unlabelled, 14 days in the diet, PLUS 1 mg/kg radiolabeled, single dose by oral gavage	The mean recovery of radioactivity 3-4 days after exposure was 90.4-104.5% following single or repeated oral doses, indicating rapid absorption, distribution, and elimination. Bioaccumulation of the parent compound and metabolites is low. There were no major sex- or dose-related differences in absorption, distribution, or elimination. Elimination occurred primarily by biliary excretion: recovery of the administered dose occurred mainly in the bile (79.1-87.1%) 3 days after exposure and mostly in the feces (78.7-94.4%) 4 days after exposure. In contrast, radioactivity recovery in the urine was 3.2-11.5% at 3 and 4 days after exposure. Extensive metabolism occurred; numerous metabolites were found in the feces and urine. There is a dose-related difference in metabolism. A higher amount of parent compound was found in the feces following the single high dose compared to the single or repeated low dose(s), which suggests that saturation might be occurring at the high dose.
870.7485	Metabolism and pharmacokinetics – rat (supplemental)	46473401	1) 1 mg/kg radiolabelled, single dose by oral gavage, urine and feces collection up to 48 hrs; 2) 100 mg/kg radiolabelled, single dose by oral gavage, urine and feces collection up to 72 hrs; 3) 100 mg/kg radiolabelled single dose by oral gavage, urine and feces collection 72-96 hrs.	Evaluation of 1,2,4-triazole levels in urine and feces occurred at very low levels (2.48% AD, males and 1.0% AD, females). Alanine and acetic acid conjugates were not detected.

Table 4.2 - Toxicity Profile of Fenbuconazole Technical				
Guideline No.	**Study Type**	**MRID**	**Doses**	**Results**
870.7600	Dermal penetration - rat	41875019	0, 0.125, 1.25 or 12.5 mg/kg **Note:** End-use product (23.1%) was tested	Mean % of the dose absorbed (sum of urine, feces, carcass, and skin) after 10 hrs of exposure: 0.125 mg/kg: 4.25% 1.25 mg/kg: 2.08% 12.5 mg/kg: 0.45%

Attachment 3. Endpoint Selection Table

Table 4.3.1 Summary of Toxicological Doses and Endpoints for Fenbuconazole for Use in Dietary Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (General Population, including Infants and Children)	An appropriate dose and endpoint were not identified for this population group.			
Acute Dietary (Females 13-49 years of age)	NOAEL = 30 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Acute RfD = 0.3 mg/kg/day Acute PAD= 0.3 mg/kg/day	**Developmental rat study** Developmental LOAEL = 75 mg/kg/day based on increased resorptions and decreased live fetuses per dam.
Chronic Dietary (All Populations)	NOAEL= 3 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Chronic RfD = 0.03 mg/kg/day cPAD = 0.03 mg/kg/day	**Combined chronic toxicity/ carcinogenicity - Rat** LOAEL = 30.6/43.1 (M/F) mg/kg/day based on decreased body weight gain, increased thyroid weight, and histopathological lesions in the liver and thyroid gland
Cancer (oral, dermal, inhalation)	**Classification: Group C, probable human carcinogen.** This classification is based on increased incidence of hepatocellular adenomas and carcinomas in male and female mice and thyroid follicular adenomas and combined adenomas/carcinomas in male rats. Quantification of risk was derived using combined hepatocellular adenomas/carcinomas in female mice. The upper bound estimate of unit risk, Q_1^* $(mg/kg/day)^{-1}$ is 3.59×10^{-3} in human equivalents.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. N/A = not applicable.

Table 4.3.2 Summary of Toxicological Doses and Endpoints for Fenbuconazole for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal All Durations	No endpoint of concern was identified, based on a lack of hazard via the dermal route.			

Table 4.3.2 Summary of Toxicological Doses and Endpoints for Fenbuconazole for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Inhalation Short-Term (1-30 days) and Intermediate-term (1-6 months)	Oral study NOAEL= 5.1 mg/kg/day [Inhalation toxicity assumed equivalent to oral toxicity]	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	**90-day oral toxicity - Rat** LOAEL = 25.3/31/1 (M/F) mg/kg/day based on decreased body weight gain, clinical chemistry changes, and histopathological lesions in the liver and thyroid gland.
Cancer (oral, dermal, inhalation)	**Classification: Group C, probable human carcinogen.** This classification is based on increased incidence of hepatocellular adenomas and carcinomas in male and female mice and thyroid follicular adenomas and combined adenomas/carcinomas in male rats. Quantification of risk was derived using combined hepatocellular adenomas/carcinomas in female mice. The upper bound estimate of unit risk, Q_1* $(mg/kg/day)^{-1}$ is 3.59×10^{-3} in human equivalents.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Attachment 4. International Residue Limit Status

Fenbuconazole (129011; 10/10/2012)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US	Canada		Mexico[2]	Codex[3]
40 CFR § 180.480 Plant/Livestock: combined residues of the fungicide fenbuconazole, alpha-[2-(4-chlorophenyl)- ethyl]-alpha-phenyl-3-(1H-1,2,4-triazole)- 1-propanenitrile, and its metabolites RH-9129, cis-5-(4-chlorophenyl)- dihydro-3-phenyl-3-(1H-1,2,4- triazole-1-ylmethyl)-2-3 H-furanone, and RH-9130, trans-5-(4-chlorophenyl)dihydro-3-phenyl-3- (1H-1,2,4-triazole-1-ylmethyl)-2-3 H- furanone, expressed as fenbuconazole	α-[2-(4-chlorophenyl)ethyl]-α-phenyl-1*H*-1,2,4-triazole-1-propanenitrile, including the metabolites *cis*-5-(4-chlorophenyl)-dihydro-3-phenyl-3-(1*H*-1,2,4-triazol-1-ylmethyl)-2-3*H*-furanone and *trans*-5-(4-chlorophenyl)-dihydro-3-phenyl-3-(1*H*-1,2,4-triazol-1-ylmethyl)-2-3*H*-furanone			Fenbuconazole. The residue is fat-soluble.
Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[2]	Codex[3]
Pepper	1.0			0.6 peppers 2 peppers Chili, dried (draft MRL awaiting ARfD evaluation)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US	Canada		Mexico[2]	Codex[3]
Completed: M. Negussie; 10/12/2012				

[1] Includes only commodities ofinterest for this action. Tolerance values should be the HED recommendations and not those proposed by the applicant.[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes. [3] * = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample. MRLs indicated as proposed have not been finalized by the CCPR and the CAC.